REMARKS

The Office Action

Claims 55-71 are pending. Claims 58 and 66 are objected to for informalities. Claims 55-63, 65-68, 70, and 71 stand rejected for lack of enablement. Claims 55-71 stand rejected for indefiniteness. Claims 55-71 stand further rejected for obviousness in view of Sassen et al. (Cardiovasc. Drugs Ther. 1994, 8:179-191; hereafter "Sassen"), Vane et al. (Circulation, 1991; 84:2588-2590; hereafter "Vane"), Lee et al. (Am. J. Cardiol. 1994, 73:1037-1040; hereafter "Lee"), Watts et al. (Lancet 1992, 339:563-569; hereafter "Watts"), and Demopulos et al. (U.S. Patent No. 5,800,385; hereafter "Demopulos").

Claims Objections

Claim 58, from which claim 66 depends, has been amended as the Examiner suggested, and the objection may be withdrawn.

Rejections under 35 U.S.C. 112, first paragraph

Claim 55-60, 62, 63, 65-68, 70, and 71 stand rejected for lack of enablement on the basis that "the specification, while being enabling for cholesterol synthesis or transfer inhibitor[s] disclosed in page 7 in the specification, line 3-12, does not reasonably provide

enablement for other cholesterol synthesis or transfer inhibitors." Applicants respectfully disagree.

The Office states:

> Applicant fails to set forth the criteria that defines neither a "cholesterol synthesis inhibitor" or "cholesterol transfer inhibitor". Given that there is no common core structural, physical, or chemical properties of the cholesterol synthesis inhibitors or cholesterol transfer inhibitors have been provided, the skilled artisan would be required to conduct undue experimentation in order to select compounds that will be useful in the practice of the instant invention.

Applicants assert that "cholesterol synthesis or transfer inhibitors" are classes of compounds well known in the medical arts. As stated in M.P.E.P. § 2164.01, "[a] patent need not teach, and preferably omits, what is well known in the art (emphasis added, citation omitted). As evidence of the well understood meaning of these terms, Applicants enclose a passage from Stryer (*Biochemistry*, 4th ed. Freeman: New York, 1995 pp. 701-702) and abstracts from Schmidt et al. (*Blood Coagul. Fibrinolysis* 1993, 4:173-175), Yanagita et al. (*Clin. Ther.* 1994, 16:200-208), and Bisgaier (*Lipids* 1994, 29:811-818) to illustrate compounds of this class and the use of the terms in the art. No further teaching in Applicants' specification is required to identify compounds falling within this family, and the selection of a particular cholesterol synthesis or transfer inhibitor for a particular patient is well within the ability of medical practitioners. The rejection of claims 55-60, 62, 63, 65-68, 70, and 71 for lack of enablement may be withdrawn.

Claims 60 and 61 stand rejected for lack of enablement because "the specification, while being enabling for fish oil does not reasonably provide enablement for other marine lipids." Applicants traverse this rejection.

The Office states that "[t]here is no adequate direction provided by the applicant as to how to select other marine lipids which would be suitable for the use in the practice of the instant invention." Applicants disagree. Applicants have disclosed the active ingredients in the marine lipid – eicosapentaenoic acid or docosapentaenoic acid – and have taught the basis for the selection of a marine lipid, i.e., one that contains at least one of these active ingredients. In addition, Sassen states:

> The very long chain fatty acids from the n-3 family, eicosapentaenoic (20:5n-3 or EPA), docosapentaenoic (22:5n-3 or DPA) and docosahexaenoic (22:6n-3 or DHA) are synthesized by algae and phytoplankton, organisms that are at the bottom of the marine food chain. All marine life may therefore ultimately be enriched with these fatty acids... (emphasis added) (pg. 180, col. 1)

One skilled in the art would therefore expect that most marine lipids would contain at least one of the active ingredients, and the rejection of claims 60 and 61 for lack of enablement may be withdrawn.

Rejections under 35 U.S.C. 112, second paragraph

Claims 55-71 are rejected for indefiniteness for reciting "compound comprising" and "cholesterol synthesis or transfer inhibitor."

Regarding the term "compound," Applicants have amended claim 55 to change "compound" to "composition," and this basis for the rejection may be withdrawn. Regarding the term "cholesterol synthesis or transfer inhibitor," as stated above, cholesterol synthesis inhibitors and cholesterol transfer inhibitors refer to classes of compounds well known in the medical arts. One skilled in the art would thus understand the meaning and scope of these terms. The rejection for indefiniteness may be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 55-71 stand rejected for obviousness over Sassen, Vane, Lee, Watts, and Demopulos. Applicants respectfully traverse this rejection.

Claims 55, from which all other claims depend, recites:

> 55. A method for reducing coronary artery stenosis by at least 20% in a mammal comprising the administration to said mammal of a combination of (a) a composition comprising eicosapentaeneoic acid or docosahexaeneoic acid and (b) a cholesterol synthesis or transfer inhibitor, in combination with limiting fat or cholesterol intake, whereby a serum LDL concentration of less than or equal to 70 mg/dl is achieved. (emphasis added)

The present claims are thus all directed to a combination therapy requiring three components: (1) eicosapentaeneoic acid or docosahexaeneoic acid, (2) a cholesterol synthesis or transfer inhibitor, and (3) limiting fat or cholesterol intake.

M.P.E.P. § 2142 states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991).

This standard has not been met in this case. Applicants assert that the prior art provides neither the suggestion nor the motivation to combine the cited references, nor does the combination of the cited references teach or suggest all of the limitations of the claimed invention. Moreover, the cited references provide no reasonable expectation that such a combination would have led to success.

The references do not teach or suggest all of the claim limitations.

As the courts have held, to render a combination obvious, the prior art must do more than disclose the individual elements; the prior art must suggest the claimed combination as well.

For example, in the case of *In re Fromson*, 755 F.2d 1549, 225 U.S.P.Q. 26 (Fed. Cir. 1985), the claimed invention was a photographic plate for use in planographic printing. The district court held the patent invalid for obviousness, finding that "the Fromson patent is a combination patent comprised of old elements." The Federal Circuit,

while conceding that the prior art disclosed all of the individual elements of the invention, reversed, stating:

> At no point did the court indicate, nor does the record indicate, a basis on which it can be said that the making of that combination would have been obvious when it was made.... The critical inquiry is whether "there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination." (emphasis in the original, citing *Lindeman Maschinefabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d at 1462, 221 U.S.P.Q. at 488.) Where, as here, nothing of record plainly indicates that it would have been obvious to combine previously separate process steps into one process, it is legal error to conclude that a claim to that process is invalid under § 103.

In the present case, as in *Fromson*, the cited art discloses some of the individual elements of the claimed methods. Sassen reviews several studies on the use of fish oil for the prevention and regression of atherosclerosis. Vane discloses the use of aspirin and fish oil for the prevention of thrombosis. Lee discloses the use of pravastatin, niacin, and LDL apheresis for the prevention of restenosis after angioplasty. Watts teaches the use of a controlled diet, with or without administration of cholestyramine, for the regression of atherosclerosis. Demopulos teaches the use of a solution of various compounds, potentially including buspirone, to inhibit undesirable effects (e.g., restenosis) of cardiovascular therapeutic and diagnostic procedures. While these references teach individual elements of the claims, they do not suggest the desirability of the unique combination of the claimed method. Nothing in these references pinpoints even two of

the three important components of the claimed methods nor do these references provide a basis for choosing such elements from the therapeutic suggestions listed.

In addition, the instant claims are directed to a method for reducing stenosis by at least 20%, and the prior art does not suggest such a reduction. On this issue, the Examiner states, "Watts et al. teaches cholestyramine with lipid-lowering diet are useful in regression of atherosclerosis by 66%." This statement, however, is incorrect. The 66% referred to in Watts is the percentage of patients whose restenosis did not progress. The actual reduction in stenosis reported by Watts is given in Table IV on page 565. This table lists only 1.1% (diet only) and 1.9% (diet plus cholestyramine) reductions in stenosis after treatment, which is significantly lower than the 20% required by the instant claims.

There is no motivation to combine the references.

Moreover, nothing in the cited references indicates that it would have been obvious to combine the therapeutic agents and behavioral modifications taught by the cited art. Indeed, the only basis for the combination of the cited art currently made of record is the assertion in the Office Action that "all the agents herein are known to prevent or treat restenosis or cause vasodilation." This statement, without further factual basis, clearly does not support a rejection under 35 U.S.C. § 103. Furthermore, even if the references were "properly combined," that does not establish a case of obviousness for the presently claimed invention. Because these references suggest a number of

possible therapeutic steps, leading to a substantial number of possible specific combinations, some suggestion must also exist in the references for choosing and combining the particular elements of the present method from the wide variety of suggested approaches. And, as is discussed above and in further detail below, no such suggestion is present.

In addition, of the two cited references that disclose treatments using fish oil, neither provides motivation for use in a therapy designed to reduce stenosis. Regarding the Sassen reference, the Examiner states:

> Sassen et al. teaches fish oil, which contains eicosapentaenoic acid and docosahexaenoic acid, can cause atherosclerotic lesion regression and prevent progression of atherosclerosis.

In making this assertion, the Examiner has ignored the studies detailed by Sassen that do not show any effects of fish oil on stenosis. For example, Sassen states:

> Fincham et al. ... found that in the African green monkey[,] fish oil ... did not cause regression of coronary atherosclerosis and, if anything, worsened aortic atherosclerosis... (emphasis added) (pg. 187, col. 1)

Furthermore, Sassen states:

> Maybe it is also time to temper the overrated expectations of the therapeutic effect of n-3 fatty acids. In this respect, it is of interest to note that also the capability of n-3 fatty acid-rich diets to reduce the incidence of ischemic heart disease has been questioned. (pg. 188, col. 1)

Sassen goes on to undermine the original basis for considering fish oil as a possible treatment, namely that it is diet and not genetics that predispose Eskimos to low incidence of ischemic heart disease (pg. 188, col. 1). Thus, one skilled in the art would not be

motivated by reading Sassen to use fish oil in a combination therapy, since Sassen questions the efficacy and underlying assumptions of the treatment.

The Vane reference is cited as teaching that "50-1,300mg/day of Aspirin plus fish oil are useful in vasodilatation and platelet inhibition." Contrary to the Examiner's assertion, Vane does not teach that fish oil and aspirin are useful for vasodilatation. While Vane teaches that thromboxane A_2 is a vasoconstrictor and that prostaglandin $I_{2\alpha}$ is a vasodilator, it fails to provide any teachings on the vasodilatation effects of the equivalent prostaglandins produced from fish oil. Thus, Vane only teaches the effects of fish oil on platelet aggregation and is silent on any possible effects on stenosis.

There is no expectation of success.

The case law is clear that, for an invention to be obvious, there must also be some suggestion of a reasonable expectation of success. This suggestion must be found in the prior art, and not in the present specification. As the Federal Circuit held in *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991),

> Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be

> founded in the prior art, not in the applicant's disclosure. (emphasis added; citations omitted)

Here, the Examiner seems to suggest that the prior art does provide an expectation of success, asserting that "combining two or more agents which are known to be useful to prevent or treat restenosis or cause vasodilatation individually into a method useful for reducing coronary artery stenosis or coronary artery narrowing is *prima facie* obvious."

Applicants respectfully disagree and point out that in the area of human therapy, there is rarely a reasonable expectation of success. The development of methods to treat heart disease, for example, is complicated by many factors, including the diversity of symptoms, genetic factors, health histories, and degrees of patient compliance in large populations. In addition, the fact that two different therapeutic agents can, singly, be used to treat the same condition, does not necessarily mean that the combination of those agents would be further efficacious, or indeed would be useful at all in treating that condition. In many cases, the concurrent administration of different therapeutic agents for the same condition is contraindicated, even though the agents are safe and effective when used alone. To suggest that the combination of different therapeutic agents for the same condition can be expected to yield an effective treatment for that condition is a simplification of any human treatment approach, and certainly a simplification of a treatment approach for a condition as complicated as coronary artery disease.

In sum, Applicants submit that nowhere in the cited references is a *prima facie* case of obviousness for the methods of these claims established. The references, while providing a list of therapeutics and behavioral modifications, do not teach the unique combinations of claims 55-71, nor do they provide a reasonable expectation of their success. The § 103 rejection should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a petition to extend the period for reply for two months, to and including July 26, 2002. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 25 July 2002

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Version with Markings to Show Changes Made

Marked-up versions of claims 55 and 58-60 are as follows.

55. (Amended) A method for reducing coronary artery stenosis by at least 20% in a mammal comprising the administration to said mammal of a combination of (a) a composition [compound] comprising eicosapentaeneoic acid or docosahexaeneoic acid and (b) a cholesterol synthesis or transfer inhibitor, in combination with limiting fat or cholesterol intake, whereby a serum LDL concentration of less than or equal to 70 mg/dl is achieved.

58. (Amended) The method of claim 55, wherein said combination further comprises aspirin.

59. (Amended) The method of claim 55, wherein said composition [compound] comprising eicosapentaeneoic acid or docosahexaeneoic acid is administered at greater than or equal to 5 g/day.

60. (Amended) The method of claim 55, wherein said composition [compound] is a marine lipid.

Effect of treatment with a hydroxymethylglutaryl coenzyme A reductase inhibitor on fasting and postprandial plasma lipoproteins and cholesteryl ester transfer activity in patients with NIDDM.

Bhatnagar D, Durrington PN, Kumar S, Mackness MI, Dean J, Boulton AJ.

University Department of Medicine, Manchester Royal Infirmary, U.K.

Patients with non-insulin-dependent diabetes mellitus (NIDDM) have a greater risk of developing coronary heart disease than would be expected from a similar degree of hyperlipidemia in nondiabetic populations. Accelerated transfer of cholesteryl esters (CET) from high-density lipoprotein (HDL) to low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL), a process that is associated with atherosclerosis, may be a possible explanation for this. CET, plasma lipoprotein concentration, and mass in the fasting and postprandial state have been examined in 31 hyperlipidemic patients with NIDDM before and after 8 weeks of treatment with the hydroxymethylglutaryl (HMG)-coenzyme A (CoA) reductase inhibitor pravastatin in a double-blind, placebo-controlled, parallel group study. Body mass index, glycemic control, and blood pressure remained unaltered during the study period. Compared with placebo, pravastatin decreased fasting serum cholesterol ($P < 0.001$) and LDL cholesterol ($P < 0.002$) levels. The high basal CET (34.4 +/- 13.1 nmol.ml-1.h-1) was decreased significantly by pravastatin treatment (27.5 +/- 13.7 nmol.ml-1.h-1, $P = 0.013$). There was a fall in the total cholesterol, free cholesterol, and phospholipid content of the Sf 0-12, 20-60, and 60-400 lipoproteins (all $P = 0.001$). Lecithin: cholesterol acyl transferase activity was not altered. The postprandial increase in VLDL

cholesterol 5 h after a standardized mixed meal was attenuated after pravastatin treatment (P = 0.011). Inhibition of hepatic cholesterol synthesis with an HMG-CoA reductase inhibitor in hyperlipidemic patients with NIDDM decreased serum cholesterol content of triglyceride-rich lipoprotein, thereby decreasing the transfer of cholesteryl ester from HDL to LDL and VLDL.

Publication Types:
- Clinical Trial
- Controlled Clinical Trial

PMID: 7698516 [PubMed - indexed for MEDLINE]

1: Clin Ther 1994 Mar-Apr;16(2):200-8

Effects of simvastatin, a cholesterol synthesis inhibitor, on phosphatidylcholine synthesis in HepG2 cells.

Yanagita T, Yamamoto K, Ishida S, Sonda K, Morito F, Saku K, Sakai T.

Department of Applied Biological Sciences, Saga University, Japan.

The effects of the addition of a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, simvastatin, to the medium on sterol synthesis and phosphatidylcholine (PC) synthesis were studied in HepG2 cells. The cells were cultured with simvastatin at concentrations of 10(-7) and 10(-6) mol/L for 6 hours, and radioactive lipid precursors were added 1 hour before harvesting. Simvastatin inhibited cholesterol synthesis from [14C]acetate in a dose-dependent manner. It also decreased the incorporation of [14C]choline into PC by 30%; this decrease was accompanied by a decrease in phosphocholine cytidylyltransferase activity in cell homogenates. Simvastatin had no significant effects on the incorporation of [3H]glycerol into phospholipids. These data indicate that simvastatin has two different functions: inhibition of HMG-CoA reductase and depression of de novo synthesis of PC via the cytidine diphosphate-choline pathway, which, in turn, may result in a decrease in plasma lipid levels.

PMID: 8062316 [PubMed - indexed for MEDLINE]

1: Blood Coagul Fibrinolysis 1993 Feb;4(1):173-5

Elevated lipoprotein(a) is lowered by a cholesterol synthesis inhibitor in a normocholesterolaemic patient with premature myocardial infarction.

Schmidt HH, Wagner S, Manns MP.

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We have identified a 37-year-old patient suffering from two myocardial infarctions, with a markedly elevated lipoprotein(a) [Lp(a)] level and normal levels of cholesterol and triglycerides. Clinically this patient presented with xanthelasma and arcus lipoides corneae. After treatment with a cholesterol synthesis inhibitor (Pravastatin), the Lp(a) concentration in this patient was reduced significantly. This case report supports the hypothesis that elevated Lp(a) is an independent risk factor for coronary artery disease. The effect of the cholesterol synthesis inhibitor on Lp(a) may be due to the upregulation of the LDL-receptor, suggesting a role for LDL receptor in Lp(a) catabolism.

PMID: 8457647 [PubMed - indexed for MEDLINE]

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1: Lipids 1994 Dec;29(12):811-8

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Cholesteryl ester transfer protein inhibition by PD 140195.

Bisgaier CL, Essenburg AD, Minton LL, Homan R, Blankley CJ, White A.

Department of Atherosclerosis Therapeutics, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan 48105.

The presence of plasma cholesteryl ester transfer protein (CETP) activity may be atherogenic, and, therefore, strategies to inhibit its activity or production may result in a beneficial effect on lipoprotein profiles and the disease process. The current report describes 4-phenyl-5-tridecyl-4H-1,2,4- triazole-3-thiol (PD 140195), a novel CETP inhibitor. The concentration-dependent inhibition of CETP by PD 140195 and the inhibitory monoclonal antibody (Mab) TP2 is demonstrated in a variety of in vitro assay systems. Molecular models of PD 140195 suggest a spatial mimicry of the cholesteryl ester structure. Despite the structural similarity, kinetic studies with a fluorescent cholesteryl ester analog suggest that the inhibition of transfer is not competitive. PD 140195 also selectively inhibited cholesteryl ester but not triglyceride transfer, while the Mab TP2 blocked CETP transfer of both. Studies were carried out to determine whether CETP inhibition observed in vitro could also be demonstrated in vivo. When PD 140195 was intravenously infused to anesthetized rabbits (up to 20 mg/kg), only transient CETP inhibition was observed. In vitro reconstitution studies in the presence of bovine serum albumin resulted in marked reduction of PD 140195 inhibitory activity. Thus, the low activity of PD 140195 in whole plasma probably results from binding to other plasma proteins.